Remarks

Status of the Claims

Claims 1, 28, and 53 are presently amended. Claims 62 – 67 are new. Claims 5, 7, 11-19, 21, 22, 24, 26, 29, 32, 36-44, 47, 49, 51, and 55 have been canceled. Claims 1-4, 6, 8-10, 20, 23, 25, 27, 28, 30, 31, 33-35, 45, 46, 48, 50, and 52 – 54, and 56 - 67 are presently pending. Claims 56 – 61 are withdrawn.

Claims 1 and 28 have been amended to recite the following definitions: L is –C(O)-; W is $-N(R^5)(R^6)$; R^4 is $-CH_2$-O-Ph, where Ph is an optionally substituted phenyl; and R^6 is optionally substituted aryl C_{1-6}alkyl or optionally substituted heterocyclyl C_{1-6}alkyl Support for the amendments can be found throughout the application as filed, for example, see, original claims 5, 7, 12, 23, 25, 29, 32, 37, 48 and 50, and the compounds of Table 2.

New claims 62 and 65 are supported by paragraph [0142] – [0145] of the application as filed. New claims 63, 64, 66, and 67 are supported by compounds throughout the application as filed, for example, in the following compounds of Table 2:

1	19	39	57	77	95	116	138	156	176	194	212
2	20	40	58	79	96	119	139	157	177	195	213
3	21	41	60	80	97	120	140	158	178	196	216
4	23	42	61	81	98	121	142	159	179	197	218
5	24	43	63	83	99	122	143	160	180	199	219
6	26	44	64	84	100	123	145	162	181	200	220
7	28	45	65	85	102	124	146	163	182	201	222
9	30	46	66	86	103	126	147	164	183	202	223
10	31	47	68	87	104	127	148	165	185	203	224
11	32	48	69	88	105	128	149	166	186	204	225
12	33	49	70	89	106	130	150	167	187	205	226
13	34	51	71	90	107	131	151	170	188	206	227
14	35	52	73	91	108	132	152	171	189	207	228
15	36	53	74	92	112	133	153	172	190	209	230
17	37	54	75	93	113	135	154	174	191	210	231
18	38	56	76	94	115	137	155	175	193	211	233

234	242	249	255	262	269	275	283	290	296	310
235	243	250	257	264	270	278	285	291	297	311
237	244	251	258	265	271	279	286	292	299	
238	245	252	259	266	272	280	287	293	302	
240	246	253	260	267	273	281	288	294	306	
241	247	254	261	268	274	282	289	295	308	

The present claim amendments do not constitute new matter. All claim amendments and cancellations are made without prejudice; Applicants reserve the right to pursue any and all canceled subject matter via continuing and/or divisional applications.

Rejections of under 35 U.S.C. § 112, 1st paragraph

(a) Rejection of claims 1, 28, and 55

Claims 1, 28, and 55 presently stand rejected for allegedly being not enabled for the claimed prodrugs and metabolites. Applicants respectfully traverse. However, in an effort to advance prosecution, claim 55 has been canceled and claims 1 and 28 have been amended to remove the term "prodrugs." Applicants respectfully request reconsideration and withdrawal of the rejection.

(b) Rejection of claims 1 – 12, 20 – 21, 27-37, 45-56, 52, and 54-55

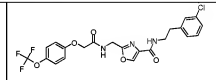
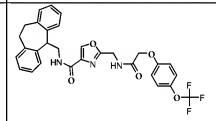
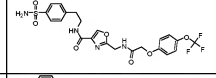
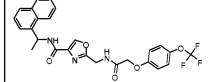
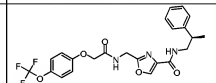
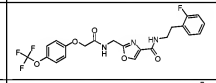
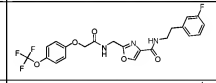
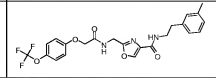
Claims 1 – 12, 20 – 21, 27-37, 45-56, 52, and 54-55 presently stand rejected for allegedly being not enabled for the compounds where R^4 is not "-CH_2CH_2-cyclic (i.e. phenyl, aryl or heterocyclic moiety)" and R^6 is not "-CH_2-O-phenyl optionally substituted." *Action*, page 8. Applicants respectfully traverse.

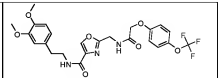
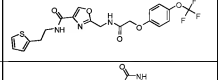
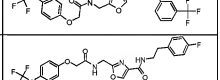
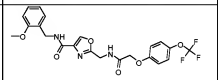
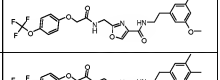
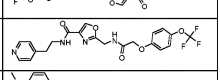
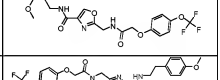
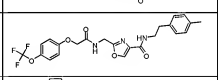
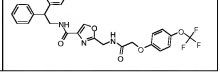
As an initial matter, it appears that the Office has confused the definition recited for each variable. Applicants note that it is the R^4 position that is generally of the formula "-CH_2-O-phenyl optionally substituted," and R^6 is generally of the formula "-CH_2CH_2-cyclic (i.e. phenyl, aryl or heterocyclic moiety)" in the instant compounds.

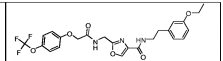
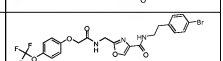
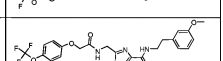
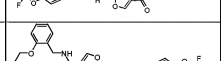
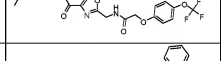
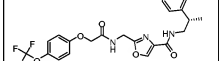
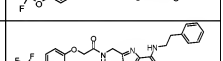
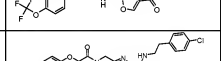
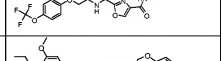
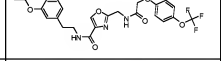
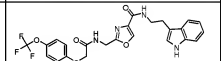
In an effort to advance prosecution, and without acquiescing to the instant rejection, Applicants have amended independent claims 1 and 28 to those compounds where L is –C(O)-; W is –N(R^5)(R^6); R^4 is –CH_2-O-Ph, where Ph is an optionally substituted phenyl (as suggested by the Examiner); and R^6 is optionally substituted aryl $C_{1\text{-}6}$alkyl or optionally substituted

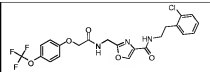
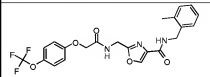
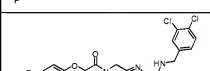
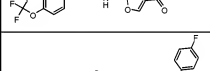
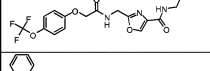
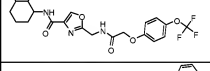
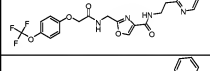
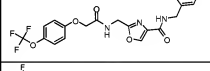
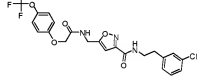
heterocyclyl C_{1-6}alkyl (which is essentially the subject matter of original claims 23, 25, 46, & 48).

In making the present rejection, the Office has stated that "[t]he nature of the invention is a thiazole compound." This is incorrect. For example, Applicants note the following compounds from Table 2 of the application as filed are not thiazoles:

31	N-[2-(3-chlorophenyl)ethyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
38	N-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylmethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
92	N-{2-[4-(aminosulfonyl)phenyl]ethyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
99	N-(1-naphthalen-1-ylethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
128	N-[(2R)-2-phenylpropyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
143	N-[2-(2-fluorophenyl)ethyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
148	N-[2-(3-fluorophenyl)ethyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
151	N-[2-(3-methylphenyl)ethyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	

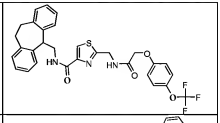
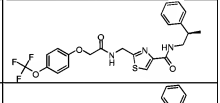
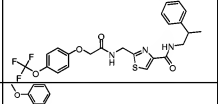
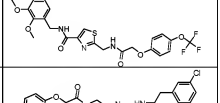
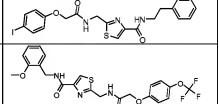
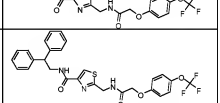
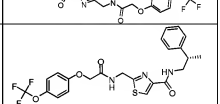
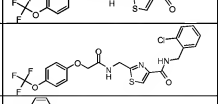
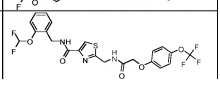
155	N-{2-[3,4-bis(methyloxy)phenyl]ethyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
159	N-[2-(2-thienyl)ethyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
181	2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-N-{2-[3-(trifluoromethyl)phenyl]ethyl}-1,3-oxazole-4-carboxamide	
201	N-[2-(4-fluorophenyl)ethyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
203	N-{[2-(methyloxy)phenyl]methyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
207	N-{2-[3,5-bis(methyloxy)phenyl]ethyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
211	N-[2-(3,4-dimethylphenyl)ethyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
219	N-(2-pyridin-4-ylethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
223	N-{[2,3-bis(methyloxy)phenyl]methyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
224	N-{2-[4-(methyloxy)phenyl]ethyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
225	N-[2-(4-methylphenyl)ethyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
226	N-(2,2-diphenylethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	

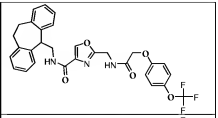
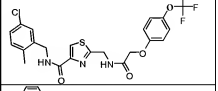
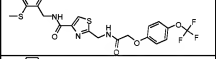
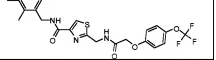
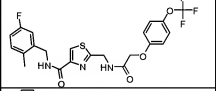
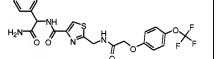
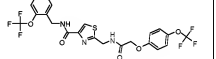
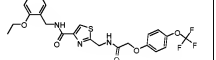
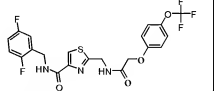
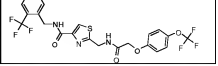
230	N-{2-[3-(ethyloxy)phenyl]ethyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
231	N-[2-(4-bromophenyl)ethyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
234	N-{2-[3-(methyloxy)phenyl]ethyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
235	N-{[2-(ethyloxy)phenyl]methyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
240	N-[(2S)-2-phenylpropyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
242	N-(2-phenylethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
246	N-[2-(4-chlorophenyl)ethyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
250	N-{2-[3-(ethyloxy)-4-(methyloxy)phenyl]ethyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
251	N-[2-(1H-indol-3-yl)ethyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
259	N-(2-phenylpropyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
261	N-[(2-chlorophenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	

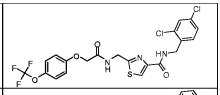
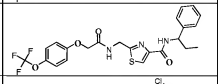
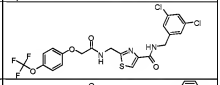
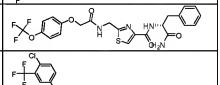
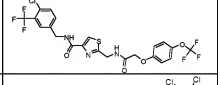
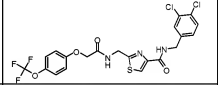
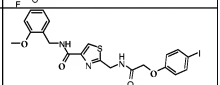
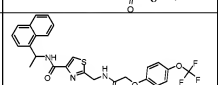
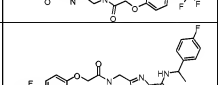
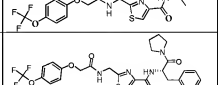
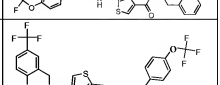
273	N-[2-(2-chlorophenyl)ethyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
288	N-[(2-methylphenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
291	N-[(3,4-dichlorophenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
292	N-[(4-fluorophenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
293	N-(1,2,3,4-tetrahydronaphthalen-1-yl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
296	N-(2-pyridin-2-ylethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
297	N-(phenylmethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
299	N-[2-(3-chlorophenyl)ethyl]-5-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)isoxazole-3-carboxamide	
306	N-[2-(3-chlorophenyl)ethyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1H-imidazole-4-carboxamide	

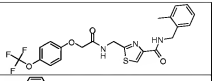
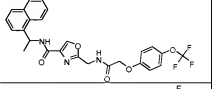
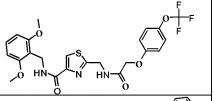
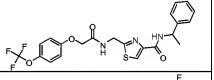
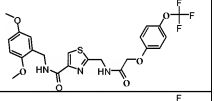
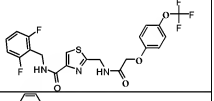
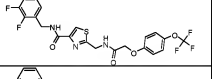
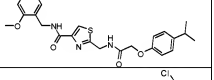
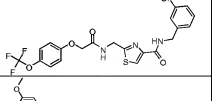
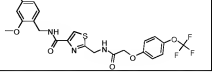
Further, the Office stated that "[i]n all of the species and examples in the specification R4 [*sic*, R6] is always $-CH_2CH_2$-cyclic optionally substituted …." This is incorrect. For example,

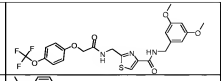
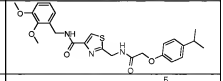
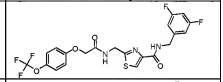
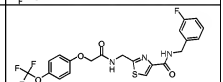
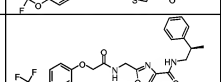
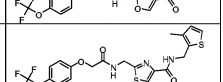
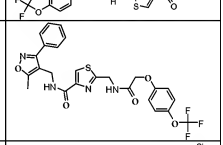
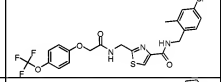
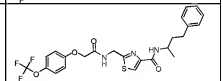
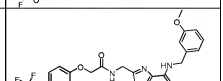
Applicants note the following compounds from Table 2 of the application as filed have R^6 groups other than just "–CH_2CH_2-cyclic optionally substituted ":

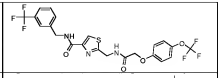
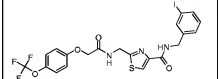
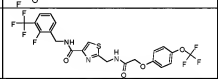
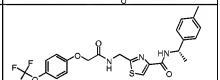
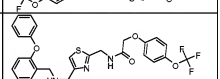
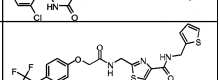
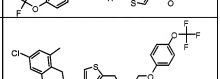
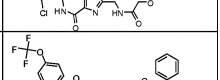
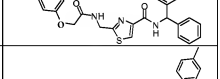
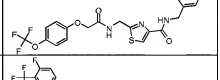
4	N-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylmethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
6	N-[(2R)-2-phenylpropyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
7	N-(2-phenylpropyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
11	N-{[2,3-bis(methyloxy)phenyl]methyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
16	N-[2-(3-chlorophenyl)ethyl]-2-[({[(4-iodophenyl)oxy]acetyl}amino)methyl]-1,3-thiazole-4-carboxamide	
17	N-{[2-(methyloxy)phenyl]methyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
18	N-(2,2-diphenylethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
26	N-[(2S)-2-phenylpropyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
32	N-[(2-chlorophenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
34	N-({2-[(difluoromethyl)oxy]phenyl}methyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	

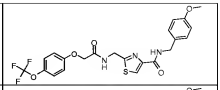
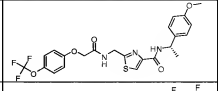
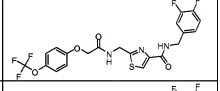
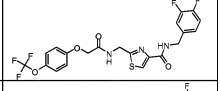
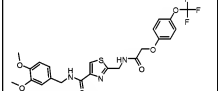
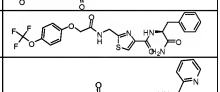
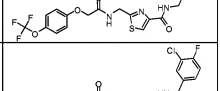
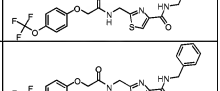
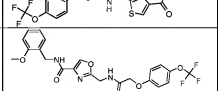
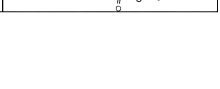
38	N-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylmethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
39	N-[(5-chloro-2-methylphenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
41	N-{[2-(methylthio)phenyl]methyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
46	N-[(2,3-dimethylphenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
47	N-[(5-fluoro-2-methylphenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
54	N-(2-amino-2-oxo-1-phenylethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
57	N-({2-[(trifluoromethyl)oxy]phenyl}methyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
58	N-{[2-(ethyloxy)phenyl]methyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
61	N-[(2,5-difluorophenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
63	2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-N-{[2-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxamide	

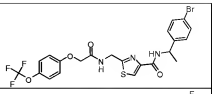
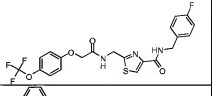
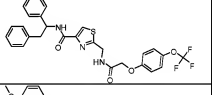
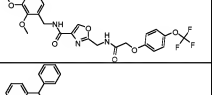
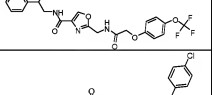
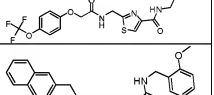
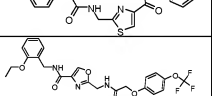
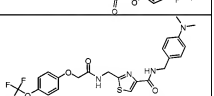
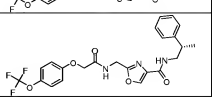
64	N-[(2,4-dichlorophenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
65	N-(1-phenylpropyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
69	N-[(3,5-dichlorophenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
70	Nalpha-{[2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazol-4-yl]carbonyl}-D-phenylalaninamide	
73	N-{[4-chloro-3-(trifluoromethyl)phenyl]methyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
75	N-[(3,4-dichlorophenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
82	2-[({[(4-iodophenyl)oxy]acetyl}amino)methyl]-N-{[2-(methyloxy)phenyl]methyl}-1,3-thiazole-4-carboxamide	
85	N-(1-naphthalen-1-ylethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
86	N-[1-(4-fluorophenyl)ethyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
91	N-[(1S)-2-oxo-1-(phenylmethyl)-2-pyrrolidin-1-ylethyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
97	N-{[2-chloro-5-(trifluoromethyl)phenyl]methyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	

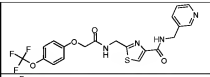
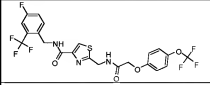
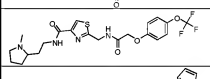
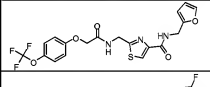
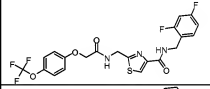
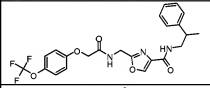
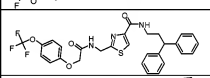
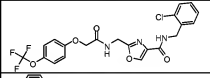
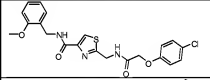
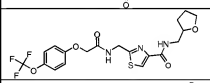
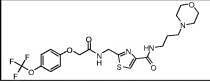
98	N-[(2-methylphenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
99	N-(1-naphthalen-1-ylethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
106	N-{[2,6-bis(methyloxy)phenyl]methyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
108	N-(1-phenylethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
112	N-{[2,5-bis(methyloxy)phenyl]methyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
115	N-[(2,6-difluorophenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
116	N-[(2,3-difluorophenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
118	2-{[({[4-(1-methylethyl)phenyl]oxy}acetyl)amino]methyl}-N-{[2-(methyloxy)phenyl]methyl}-1,3-thiazole-4-carboxamide	
119	N-[(3-chlorophenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
120	N-{[2,4-bis(methyloxy)phenyl]methyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	

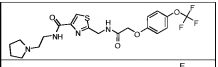
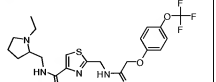
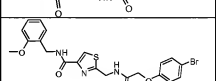
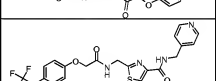
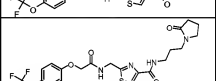
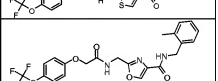
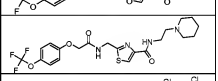
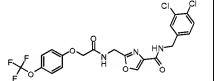
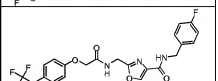
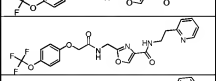
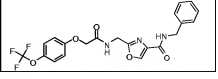
121	N-{[3,5-bis(methyloxy)phenyl]methyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
125	N-{[2,3-bis(methyloxy)phenyl]methyl}-2-{[({[4-(1-methylethyl)phenyl]oxy}acetyl)amino]methyl}-1,3-thiazole-4-carboxamide	
126	N-[(3,5-difluorophenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
127	N-[(3-fluorophenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
128	N-[(2R)-2-phenylpropyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
133	N-[(3-methyl-2-thienyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
135	N-[(5-methyl-3-phenylisoxazol-4-yl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
150	N-[(4-chloro-2-methylphenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
152	N-(1-methyl-3-phenylpropyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
154	N-{[3-(methyloxy)phenyl]methyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	

156	2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-N-{[3-(trifluoromethyl)phenyl]methyl}-1,3-thiazole-4-carboxamide	
157	N-[(3-iodophenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
158	N-{[2-fluoro-3-(trifluoromethyl)phenyl]methyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
162	N-[(1S)-1-(4-methylphenyl)ethyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
163	N-{[2-chloro-6-(phenyloxy)phenyl]methyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
164	N-(2-thienylmethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
166	N-[(2,4-dichloro-6-methylphenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
167	N-(diphenylmethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
170	N-[(4-methylphenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
174	N-{[4-fluoro-3-(trifluoromethyl)phenyl]methyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	

178	N-{[4-(methyloxy)phenyl]methyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
183	N-{(1S)-1-[4-(methyloxy)phenyl]ethyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
185	N-[(3,4-difluorophenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
186	N-{[2-(methylthio)phenyl]methyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
187	N-{[3,4-bis(methyloxy)phenyl]methyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
188	Nalpha-{[2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazol-4-yl]carbonyl}-L-phenylalaninamide	
190	N-(pyridin-2-ylmethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
191	N-[(3-chloro-4-fluorophenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
194	N-(phenylmethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
203	N-{[2-(methyloxy)phenyl]methyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	

204	N-[1-(4-bromophenyl)ethyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
206	N-[(4-fluorophenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
222	N-(1,2-diphenylethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
223	N-{[2,3-bis(methyloxy)phenyl]methyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
226	N-(2,2-diphenylethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
227	N-[(4-chlorophenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
229	N-{[2-(methyloxy)phenyl]methyl}-2-{[(naphthalen-2-ylacetyl)amino]methyl}-1,3-thiazole-4-carboxamide	
235	N-{[2-(ethyloxy)phenyl]methyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
237	N-{[4-(dimethylamino)phenyl]methyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
240	N-[(2S)-2-phenylpropyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	

241	N-(pyridin-3-ylmethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
244	N-{[4-fluoro-2-(trifluoromethyl)phenyl]methyl}-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
247	N-[2-(1-methylpyrrolidin-2-yl)ethyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
249	N-(furan-2-ylmethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
258	N-[(2,4-difluorophenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
259	N-(2-phenylpropyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
260	N-(3,3-diphenylpropyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
261	N-[(2-chlorophenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
263	2-[({[(4-chlorophenyl)oxy]acetyl}amino)methyl]-N-{[2-(methyloxy)phenyl]methyl}-1,3-thiazole-4-carboxamide	
265	N-(tetrahydrofuran-2-ylmethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
267	N-(3-morpholin-4-ylpropyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	

274	N-(2-pyrrolidin-1-ylethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
275	N-[(1-ethylpyrrolidin-2-yl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
277	2-[({[(4-bromophenyl)oxy]acetyl}amino)methyl]-N-{[2-(methyloxy)phenyl]methyl}-1,3-thiazole-4-carboxamide	
285	N-(pyridin-4-ylmethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
286	N-[3-(2-oxopyrrolidin-1-yl)propyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
288	N-[(2-methylphenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
290	N-(2-piperidin-1-ylethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-thiazole-4-carboxamide	
291	N-[(3,4-dichlorophenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
292	N-[(4-fluorophenyl)methyl]-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
296	N-(2-pyridin-2-ylethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	
297	N-(phenylmethyl)-2-({[({4-[(trifluoromethyl)oxy]phenyl}oxy)acetyl]amino}methyl)-1,3-oxazole-4-carboxamide	

Applicants note that MPEP 2164.04 states (citing *In re Marzocchi*, 169 USPQ 367, 369-

70)(emphasis in original):

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented must be taken as being in compliance with the enablement requirement of 35 U.S.C. 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on for enabling support. Assuming that sufficient reason for such doubt exists, a rejection for failure to teach how to make and/or use will be proper on that basis. *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). As stated by the court, "it is incumbent upon the Patent Office, whenever a rejection on this basis is made, to explain *why* it doubts the truth or accuracy of any statement in a supporting disclosure and to back up assertions of its own with acceptable evidence or reasoning which is inconsistent with the contested statement. Otherwise, there would be no need for the applicant to go to the trouble and expense of supporting his presumptively accurate disclosure." 439 F.2d at 224, 169 USPQ at 370.

That is, the Office must establish that one skilled in the art would reasonably doubt that the asserted compounds can be made or used as claimed. *Marzocchi* provides that the Office can support such an enablement rejection by either providing evidence that the presently claimed methods of use or preparation are "contrary to generally accepted scientific principles" or providing "evidence or reasoning which is inconsistent with the contested statement." *Id.* at 369-70. The Office has provided neither and has failed to provide a *prima facie* case that the instant claims are not enabled.

Applicants have clearly provided, in the application as filed, a description of methods suitable for preparing the instantly claimed compounds. *See*, Schemes 1 – 3, and associated discussion on pages 268 – 272 of the application as filed. Therein, a synthetic pathways for the preparation compounds of formula (I) are described. The Office has not pointed to any particular portion of the synthetic methods provided in the instant application which would give one skilled in the art reasonable doubt that the presently claimed compounds can be made as described. Nor has the Office cited any prior art to cast doubt on the expectation or ability of one skilled in the art to prepare the instantly claimed compounds.

For the preceding reasons, Applicants submit that by taking into account the scope of the claims, as amended, and in view of the numerous working examples (*e.g.,* Table 2) and synthetic guidance (e.g., Schemes 1-3) within the application as filed one skilled in the art would be able to make and use the presently claimed compounds. Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejections of under 35 U.S.C. § 102(b)

(a) Rejection of claims 1 – 12, 20 – 21, 27-37, 45-56, 52, and 54-55 over Debono *et al.* (*J. Org. Chem.* 1992, *57*, 5200).

Claims 1 – 12, 20 – 21, 27-37, 45-56, 52, and 54-55 stand rejected for allegedly being anticipated by compound 11 as disclosed in DeBono. Applicants note that as amended, the genus of claim 1 recites that R^4 is $-CH_2$-O-Ph, where Ph is an optionally substituted phenyl. The amendments to claim 1 are made without prejudice and Applicants reserve the right to pursue any and all canceled subject matter by continuing or divisional applications. The present limitation to claim 1 excludes the compounds of DeBono. Applicants respectfully request reconsideration and withdrawal of the rejection.

(a) Rejection of claims 1 – 12, 20 – 21, 27-37, 45-56, 52, and 54-55 over Hoekstra *et al.* (*Bioorg. Med. Chem. Lett.* 1998, *8*, 1649).

Claims 1 – 12, 20 – 21, 27-37, 45-56, 52, and 54-55 stand rejected for allegedly being anticipated by compounds 4 and 5 as disclosed in Hoekstra. Applicants note that as amended, the genus of claim 1 recites that R^4 is $-CH_2$-O-Ph, where Ph is an optionally substituted phenyl. The amendments to claim 1 are made without prejudice and Applicants reserve the right to pursue any and all canceled subject matter by continuing or divisional applications. The present limitation to claim 1 excludes the compounds of Hoekstra. Applicants respectfully request reconsideration and withdrawal of the rejection.

Rejection of claim 1 – 12, 20 – 21, 27-37, 45-56, 52-55 of under 35 U.S.C. § 103(a)

Claims 1 – 12, 20 – 21, 27-37, 45-56, 52 - 55 presently stand rejected for allegedly being obvious over Debono and Hoekstra (above) in view of Patani *et al.* (*Chem. Rev.* **1996**, *96*, 3147). In particular, the Office has alleged that because the instantly claimed compounds are merely "structural isomers, homologs, or bioisosteres of the prior art compounds" that "one skilled in the art would be able to make similar compounds .... [and t]he motivation would be to prepare similar compounds that are pharmacologically active compounds like the compounds of Debono/Hoekstra." *Action*, page 16. The Office concludes that the "instant obviousness rejection is based on the close structural similarity of the instantly claimed compounds to the prior art compounds and the common utility shared among the compounds." *Id.* Applicants respectfully traverse.

As an initial matter, Applicants note that the Hoekstra and Debono references, and the instant invention are concerned with targeting different biological targets. Hoekstra is concerned with thrombin receptor (PAR-1) antagonists for *blocking platelet aggregation*. *See* Hoekstra, Abstract. Debono is concerned with thiopeptide *antibiotics* produced by *Streptomyces gardneri*. *See* Debono, Abstract. In contrast, the instant invention involves compounds having activity for modulating Anaplastic Lymphoma Kinase (ALK), which can affect cell proliferation, differentiation, and migration; and programmed cell death. *See* abstract.

The Office has failed to articulate a reason why one of ordinary skill in the art would have reason to modify the compounds of Debono or Hoesktra, in general. Nor has the Office articulated a reason by one of ordinary skill in the art would have a reason to modify the compounds of Debono and Hoesktra in the particular manner necessary to arrive at the presently claimed compounds. "In cases involving new chemical compounds, it remains necessary to identify some reason that would have led a chemist to modify a known compound *in a particular manner* to establish a prima facie obviousness of a new claimed compound." *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.* 492 F.3d 1350, 1357 (Fed. Cir. 2007) (emphasis added).

In a similar rejection in *Ex parte Donde*, the Office rejected a genus of prostaglandin derivatives as obvious under 35 U.S.C. § 103(a) over a prior US patent disclosing other prostaglandins having similar structures to those claimed and the very same Patani reference for the teaching of bioisosteric replacements relied on for the present rejection. In *Donde*, the Examiner alleged that "one of ordinary skill in the art would infer that [groups that] are bioisosteres of each other and that the groups could be swapped in other molecules with a reasonable expectation that another molecule with the same utility would be generated." No. 2009-012378, slip op at 4 (B.P.A.I May 18, 2010).

In rejecting the Office's reasoning, the Board of Appeals stated the following:

> If we were to adopt the Examiner's reasoning, any substitution of any group for a known bioisostere would be prima facie obvious, whether there is any suggestion in the art to make the modification or not. But that is not the state of the law, because as noted by the Court of Appeals for the Federal Court, in order to establish a prima facie case of obviousness, there must be a reason in the prior art that would have suggested making the specific molecular modifications necessary to achieve the claimed invention. Takeda 492 F.3d at 1356.

Ex parte Donde, slip op at 6 – 7. As in *Donde*, the Office has not provided any motivation in the art to make any particular modification to the compounds of Hoeksma or Debono to arrive at the

presently claimed compounds, That is, in a situation where any of a wide variety of modification of the prior art could be made to yield alternate compounds, the Office has not provided any reason to select any of the possible changes, much less a reason to select the particular changes which would result in the presently claimed compound.

Furthermore, the presently claimed compounds have an unexpected property, the ability to modulate ALK. "From the standpoint of patent law, a compound and all of its properties are inseparable; they are one and the same thing." *In re Papesch*, 315 F.2d 381, 391 (CCPA 1963) ("[A] compound and all of its properties are inseparable [...] the patentability of the thing does not depend on the similarity of its formula to that of another compound but of the similarity of the former compound to the latter."). The cited compounds of Hoekstra and Debono and the presently claimed compounds are markedly different - the latter are ALK modulators, a property that would not have been expected by one skilled in the art at the time the instant application was filed. The cited art provides no basis for one of ordinary skill in the art to have predicted that compounds such as those presently claimed would have the property of modulating ALK.

In view of the preceding lack of motivation to select a lead compound from Hoeksma or Debono and the lack of motivation to modify the Hoeksma or Debono compounds in the particular way required to yield the claimed compounds, Applicants submit that the Office has failed to provide a *prima facie* case of obviousness and respectfully request reconsideration and withdrawal of the rejection.

If it is believed that a teleconference will advance prosecution, the examiner is encouraged to contact the undersigned as indicated below.

Respectfully submitted,

Date: November 23, 2010

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